Chapter 13
Cannabinoids in the Management of Nausea and Vomiting

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Abstract With the discovery of the endocannabinoid system, research investigating the role that this system plays in the control of nausea and vomiting has accelerated. In this chapter, we review some of the evidence in both human clinical trials literature and animal literature demonstrating the potential of cannabinoids to modify nausea and vomiting.

Introduction

Nausea and vomiting are common symptoms reported by patients. They can occur separately and together in many different diseases and are side effects of many drug treatments. Understanding the neurobiological mechanisms responsible for the sensation of nausea and for the reflex of vomiting is important for the development of antiemetic and antinausea treatments. The emetic reflex is conventionally considered to include vomiting, retching, and the more subjective sensation of nausea. However, the organization of the reflex is very complex, because although nausea, retching, and vomiting usually occur in a temporal sequence, they can be separated experimentally (Andrews and Davis, 1995). Although the physiology of vomiting is well understood, the same is not true of nausea (Andrews and Horn, 2006). Chemotherapy treatment for cancer is often accompanied by the serious side effects of nausea and vomiting which may interfere with the completion of treatment. Chemotherapy patients experience three separate types of emetic episodes: (1) acute nausea and/or vomiting that occurs within minutes to hours of receiving a dose of a toxic chemotherapy drug; (2) delayed nausea and/or vomiting that has been arbitrarily defined as emesis that begins or persists more than 24 h after chemotherapy; (3) anticipatory nausea and/or vomiting that occurs when the patient is reexposed to cues associated with the toxin. Anticipatory nausea/vomiting occurs in nearly half of the patients treated, frequently during later cycles of chemotherapy. The more intense the initial acute emetic episode is, the worse is the resultant anticipatory nausea/vomiting (Aapro et al., 1994). A major advance in the control of acute emesis in chemotherapy treatment was the finding that blockade of one subtype of the 5-hydroxytryptamine (5-HT) receptor, the 5-HT \textsubscript{3} receptor, could
suppress the acute emetic response (retching and vomiting) induced by cisplatin in the ferret and the shrew (Costall et al., 1986; Miner and Sanger, 1986; Ueno et al., 1987; Matsuki et al., 1988; Torii et al., 1991). In clinical trials with humans, the treatment with 5-HT₃ antagonists often combined with the corticosteroid, dexamethasone, during the first chemotherapy treatment has reduced the incidence of acute vomiting by 70–90% (Reynolds et al., 1991; Tsukada et al., 2001; Bartlett and Koczwara, 2002; Aapro et al., 2003; Ballatori and Roila, 2003; Hickock et al., 2003). If acute vomiting is prevented, the incidence of delayed and anticipatory vomiting is reduced (Aapro et al., 1994). However, the 5-HT₃ antagonists are less effective in suppressing acute nausea than they are in suppressing acute vomiting (Andrews and Davis, 1995; Morrow and Dobkin, 1988; Barlett and Koczwara, 2002; Ballatori and Roila, 2003; Hickok et al., 2003) and they are ineffective in reducing instances of delayed nausea/vomiting (Morrow and Dobkin, 1988; Grelot et al., 1995; Rudd and Naylor, 1996; Rudd et al., 1996; Tsukada et al., 2001; Hesketh et al., 2003) and anticipatory nausea/vomiting (Nesse et al., 1980; Morrow and Dobkin, 1988; Reynolds et al., 1991; Stockhorst et al., 1993; Ballatori and Roila, 2003; Hickok et al., 2003) when they do occur. Therefore, it is likely that another system may be involved in chemotherapy-induced nausea, delayed nausea/vomiting, and anticipatory nausea/vomiting. Two such systems include the Neurokinin 1 (NK₁) tachykinin receptors for substance P (e.g., Rudd and Naylor, 1996; Rudd et al., 1996; Hesketh et al., 2003) and the endocannabinoid system. The effect of cannabinoids on nausea and vomiting is the subject of this review.

**Antiemetic Effects of Cannabinoids in Human Clinical Trials**

The marijuana plant has been used for several centuries for a number of therapeutic results, including nausea and vomiting. Ineffective treatment of chemotherapy-induced nausea prompted oncologists to investigate the antiemetic properties of cannabinoids in the late 1970s and early 1980s. In these early studies, several clinical trials have compared the effectiveness of Δ⁹-THC with placebo or other antiemetic drugs. Comparisons of oral Δ⁹-THC with existing antiemetic agents generally indicated that Δ⁹-THC was at least as effective as the dopamine antagonist, prochlorperazine (Carey et al., 1983; Ungerleider et al., 1984; Tramer et al., 2001). Three cannabis-based medicines are available: Dronabinol™, Nabilone™, and levonantradol. A systematic review (Tramer et al., 2001) found that oral Nabilone, Dronabinol, and intramuscular levonantradol were more effective than other antiemetics after mild to moderately emetogenic chemotherapy, but were less effective after highly emetogenic chemotherapy compared with the dopamine antagonist, metoclopramide (Crawford and Buckman, 1986; Cunningham et al., 1988). Withdrawal rates from these trials indicated a narrow therapeutic dose range of effectiveness suggesting a need to carefully titrate the dose. Since these earlier trials, the more effective 5-HT₃ antagonist antiemetic drugs have been developed that reduce acute vomiting during cancer chemotherapy. Additionally, NK₁ receptor